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Safety of direct-acting oral anticoagulant (DOAC) prescribing: OpenSAFELY-TPP analysis of 20.5 million adults' electronic health records

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Abstract

Background

During the COVID-19 pandemic many patients were switched from warfarin to DOACs which require the creatinine clearance calculated to ensure the correct dose is prescribed to avoid bleeding or reduced efficacy.

Aim

To identify the study population proportion prescribed a DOAC. Of these, the proportion with recorded: weight, estimated Glomerular Filtration Rate (eGFR), creatinine, creatinine clearance (CrCl) and atrial fibrillation (AF). To analyse the proportion of patients with recorded AF and CrCl prescribed a recommended DOAC dose.

Design and Setting

A retrospective cohort study of 20.5 million adult NHS patients' electronic health records (EHRs) in England in the OpenSAFELY-TPP platform (January 2018 to February 2023).

Method

Patients on DOACs were analysed for age, sex, recorded weight, eGFR, creatinine, CrCl and AF. Prescribed DOAC doses in patients with recorded AF were compared to recommended doses for recorded CrCl and determined as either recommended, underdose or overdose.

Results

In February 2023, weight, eGFR, creatinine, CrCl, AF and, AF and CrCl were recorded in 72.8%; 92.4%; 94.3%; 73.5%; 73.9% of study population respectively. Both AF and CrCl were recorded for 56.7% of patients. Of these, 86.2% received the recommended and 13.8% non-recommended DOAC doses.

Conclusions

CrCl is not recorded for a substantial number of patients on DOACs. We recommend that national organisations tasked with safety, collectively update guidance on the appropriate weight to use in the Cockcroft-Gault equation, clarify that CrCl is not equivalent to eGFR and work with GP clinical system suppliers to standardise the calculation of CrCl in the EHR.

Key words

General practice, DOAC, creatinine clearance, COVID-19

How this fits in

DOACs require renal function tests and CrCl calculated so safe and effective doses are prescribed, but CrCl is not being recorded in a substantial number of patients. There is no national agreement on which weight to use in CrCl calculations and, where GP clinical systems have internal CrCl calculators, these are inconsistent on which weight is used. With the increasing number of people on DOACs there is an urgent need to have national agreement on which weight is used in CrCl calculations. National organisations tasked with safety should work with GP clinical systems suppliers to facilitate automated CrCl recording when renal function tests are recorded.

Introduction

During the COVID-19 pandemic many patients were switched from warfarin to a DOAC: apixaban, edoxaban, dabigatran, or rivaroxaban, to continue to keep patients on anticoagulants as safe as possible and reduce the impact on service provision to take on international normalised ratio (INR) monitoring in the community for the large number of patients who were housebound through COVID-19 infection, self-isolating and adopting social distancing strategies.¹ Compared to warfarin, DOACs require less frequent monitoring, have a faster onset of action, predictable pharmacokinetics, and fewer food and drug interactions.² Although DOACs have these advantages, their use increases the risk of bleeding and can cause serious, potentially fatal, bleeds. The Medicines Healthcare products Regulatory Agency (MHRA) warns that DOACs should be used with caution in patients at increased risk of bleeding such as in older patients, those with low body weight or renal impairment.³ In England renal function is commonly measured by eGFR.⁴ However, it is recommended that when prescribing and monitoring DOACs, renal function is assessed by calculating the CrCl using the Cockcroft-Gault method as eGFR can overestimate the renal function and increase the risk of bleeding⁴⁻⁶ People with AF are prescribed DOACs long term and so have a greater exposure time to DOACs compared to use in other indications.⁴

National clinical guidance issued during the COVID-19 pandemic suggested a process for switching from warfarin to a DOAC, which included checking the GP clinical system for urea and electrolytes (U&Es), recording weight, calculating CrCl and ensuring that the DOAC is prescribed at an appropriate dose.¹

The OpenSAFELY-TPP platform is a secure, transparent, open source software platform that allows for the analysis of 24 million NHS electronic health records, covering 40% of general practices in England. OpenSAFELY has been used to deliver urgent academic and operational NHS service research on the direct and indirect impacts of the pandemic including the changing pattern of anticoagulant use during the COVID-19 pandemic⁷ and supported a national patient safety alert with the potentially inappropriate use of DOACs in people with mechanical heart valves.⁸

With the approval of NHS England, we set out to use the OpenSAFELY-TPP platform to describe the change in DOAC prescribing since the COVID-19 pandemic, the proportion of patients prescribed a DOAC who had recorded weight, creatinine, eGFR, and CrCl in line with recommendations on calculating DOAC doses in individuals.⁴⁻⁶ For patients with a CrCl coded,

the actual DOAC dose was determined as either a recommended, higher than recommended (overdose) or lower than recommended (underdose) from the recorded CrCl.¹ We then estimated the proportion with recorded AF prescribed a non-recommended DOAC dose to assess whether patients received over or underdosing of their DOAC.

Method

Study design and population

We conducted a retrospective cohort study using the patient population within the OpenSAFELY-TPP platform between January 2018 and February 2023. The study population included all patients each month who were: registered with a TPP practice; aged between 18 and 120; who had not died before the start of the month and were prescribed a DOAC (rivaroxaban, apixaban, edoxaban, or dabigatran). Patient characteristics including sex and indication for anticoagulation were extracted for the whole study population. Weight (recorded, not recorded, <50kg, >120kg), creatinine, eGFR, CrCl (recorded, not recorded, <15ml/min), AF, AF and CrCl, and the dose of DOAC were extracted, if coded in the electronic health record, from the study population between March 2022 and February 2023 for these analyses. The proportion of patients with weight, eGFR, creatinine, and CrCl recorded were reported as a percentage and compared over the study period. For patients with recorded AF prescribed a DOAC and with a CrCl recorded, the actual DOAC dose was determined as either a recommended, higher than recommended (overdose) or lower than recommended (underdose) from the recorded CrCl.¹ (Codelists used to ascertain patients prescribed DOACs are listed in table 1.)

Table 1. DOAC dose based on renal function in patients with AF¹

| DOAC | Recommended dose | Frequency | CrCl (ml/min) | Codelist |
|-------------|------------------|-------------|---------------|--------------------------------------|
| Apixaban | 5mg | Twice daily | ≥30 | OpenCodelists: DOACs |
| | 2.5mg | Twice daily | 15-29 | |
| Dabigatran | 110mg 150mg | Twice daily | > 50 | |
| | 110mg 150mg | Twice daily | 30-50 | |
| Edoxaban | 60mg | Once daily | > 50 | |
| | 30mg | Once daily | 15 - 50 | |
| Rivaroxaban | 20mg | Once daily | ≥ 50 | |
| | 15mg | Once daily | 15 - 49 | |

Statistical analysis

Patient characteristics were summarised using descriptive statistics. The study measures are presented as percentages including the proportion of the population prescribed a DOAC (all indications); percentages were reported monthly from January 2018 to February 2023. The proportion of the population with recorded AF with each monitoring parameter measured within the last 12 months (weight, creatinine, eGFR and CrCl), and the proportion of the population with a recommended (matched), overdose or underdose DOAC dose according to CrCl in patients with recorded AF; percentages were reported monthly from March 2022 to February 2023. The percentage change in each monitoring parameter measured was computed between July 2022 and February 2023, the latest data available.

Data source

All data were linked, stored and analysed securely within the OpenSAFELY-TPP platform, <https://opensafely.org/>, containing pseudonymised data on approximately 40% of the English population, including coded diagnoses, medications and physiological parameters. No free text data are included. Detailed pseudonymised patient data is potentially re-identifiable and therefore not shared.

Software and reproducibility

We conducted data management and analysis using the OpenSAFELY software libraries, Python 3. All code for the OpenSAFELY platform is freely available under open licenses for review and reuse on GitHub (<https://github.com/opensafely>). All code for data management and analysis for this paper is freely available under open licenses for review and reuse on GitHub (<https://github.com/opensafely/doacs-covid19>).

Patient and public involvement

OpenSAFELY has a publicly available website <https://opensafely.org/> through which any patients or members of the public are invited to correspond to regarding this study or the broader OpenSAFELY project.

Results

Patient characteristics

Data were extracted for 422,539 and 430,778 adults in July 2022 and February 2023 meeting the study inclusion criteria. Table 2 provides the patient characteristics of the study population, clinical parameters recorded in the electronic health record and DOAC dose analysis in July 2022 and February 2023.

Table 2:
Patient Characteristics of DOAC study patients

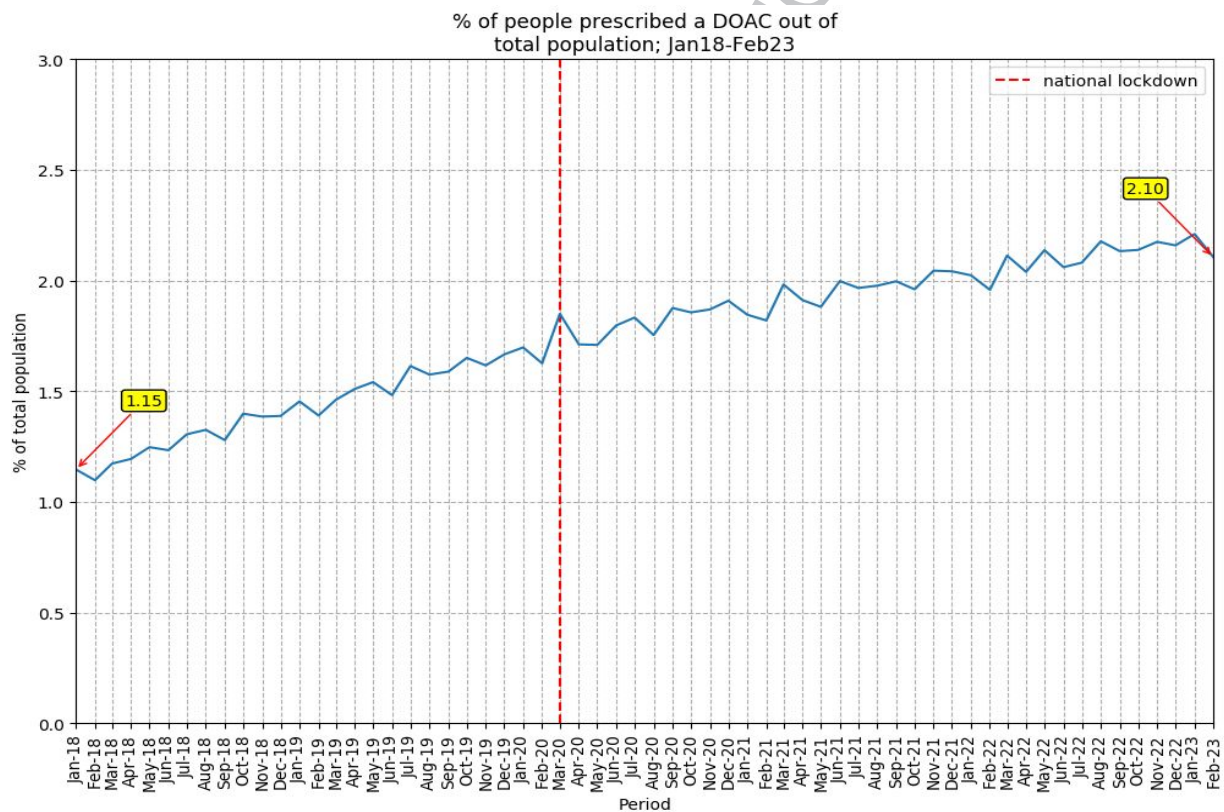
| Characteristic | Category | Jul-22 | | Feb-23 | |
|--|--------------------|---------------|---------------|---------------|---------------|
| | | n | % | n | % |
| Total patients on a DOAC | | 422539 | 100.0% | 430778 | 100.0% |
| Non calculable patients | | 878 | 0.2% | 720 | 0.2% |
| Total calculable patients | | 421661 | 99.8% | 430058 | 99.8% |
| Sex | Female | 189669 | 44.9% | 191761 | 44.5% |
| | Male | 231992 | 54.9% | 238297 | 55.3% |
| Age years) | 18-29 | 1323 | 0.3% | 1355 | 0.3% |
| | 30-39 | 4191 | 1.0% | 4246 | 1.0% |
| | 40-49 | 10747 | 2.5% | 10819 | 2.5% |
| | 50-59 | 28811 | 6.8% | 29696 | 6.9% |
| | 60-69 | 64853 | 15.3% | 49193 | 11.4% |
| | 70-79 | 139988 | 33.1% | 143070 | 33.2% |
| | 80+ | 171727 | 40.6% | 173877 | 40.4% |
| Weight | Recorded | 270696 | 64.1% | 313537 | 72.8% |
| | of which <50Kg | 9820 | 3.6% | 11822 | 3.8% |
| | of which 50-120Kg | 258211 | 95.4% | 296974 | 94.7% |
| eGFR | of which >120Kg | 2665 | 1.0% | 4741 | 1.5% |
| | Recorded | 375685 | 88.9% | 398214 | 92.4% |
| | Recorded | 383535 | 90.8% | 406335 | 94.3% |
| Serum creatinine level | Recorded | 222897 | 52.8% | 316553 | 73.5% |
| | of which <15mL/min | 2563 | 1.1% | 3196 | 1.0% |
| Serum creatinine but no creatinine clearance | Recorded | 160638 | 38.0% | 89782 | 20.8% |
| DOAC indication | AF | 313329 | 74.2% | 318169 | 73.9% |
| | Other indications | 108332 | 25.6% | 111889 | 26.0% |
| AF and CrCl | Recorded | 174056 | 41.2% | 243936 | 56.6% |
| Calculated DOAC dose compared to prescribed dose in AF where CrCl recorded | Match | 146429 | 84.4% | 208837 | 86.2% |
| | Over | 5585 | 3.2% | 6463 | 2.7% |
| | Under | 21400 | 12.3% | 26858 | 11.1% |

Supplementary Table 1 provides, for each individual DOAC, the patient characteristics of the study population, clinical parameters recorded in the electronic health record and DOAC dose analysis in July 2022 and February 2023.

Population trends in DOAC prescribing

DOAC prescribing increased from 1.15% to 2.10%, an increase of 82.6%, in the study population from January 2018 to February 2023 (Figure 1).

Figure 1. Percentage of people prescribed a DOAC out of study population (Jan 18-Feb23)



The age groups with the largest number of people on a DOAC were the 70-79 years and over 80 years age bands (Supplementary Figure 1). In February 2023, 44.5% of people prescribed a DOAC were female compared to 55.3% males (Supplementary Figure 2).

Weight, eGFR, creatinine, CrCl, AF, AF and CrCl recorded

Table 3 illustrates the percentage change in the recording of weight, eGFR, creatinine, CrCl, AF, AF and CrCl in the last 12 months which occurred in July 2022 and February 2023, the latest eight months data available. The largest increases were seen for CrCl recorded (+20.7%) and AF and CrCl recorded (+15.4%). Decreases were seen for patients with a creatinine level but no CrCl recorded (-17.2%).

Table 3. Change in recording of weight, eGFR, creatinine, CrCl in patients prescribed a DOAC (July 2022 – February 2023)

| Parameter recorded | Number (%) of patients with data recorded (July 2022) | Number (%) of patients with data recorded (February 2023) | Change in number (%) of patients (July 2022 to February 2023) |
|------------------------|---|---|---|
| Weight | 270,696 (64.1) | 313,537 (72.8) | +42,841 (+8.7) |
| eGFR | 375,685 (88.9) | 398,214 (92.4) | +22,529 (+3.5) |
| creatinine | 383,535 (90.8) | 406,335 (94.3) | +22,800 (+3.5) |
| CrCl | 222,897 (52.8) | 316,553 (73.5) | +186,344 (+20.7) |
| creatinine and no CrCl | 160,638 (38.0) | 89,782 (20.8) | -70,856 (-17.2) |
| AF diagnosis | 313,329 (74.2) | 318,169 (73.9) | +4,840 (+0.3) |
| AF diagnosis + CrCl | 174,056 (41.2) | 243,936 (56.6) | +69,880 (+15.4) |

Prescribed DOAC dosage in AF compared to recommended dose for patient's CrCl

Between March 2022 and February 2023, 74.4% to 73.9% of the study population prescribed a DOAC had a recorded diagnosis of AF. Figure 2 illustrates an increase from 36.5% to 56.7% in recorded CrCl in people prescribed a DOAC with recorded AF from March 2022 to February 2023.

Figure 2. Percentage of people prescribed a DOAC with AF and CrCl recorded in the last 12 months (March 22 to Feb 23)

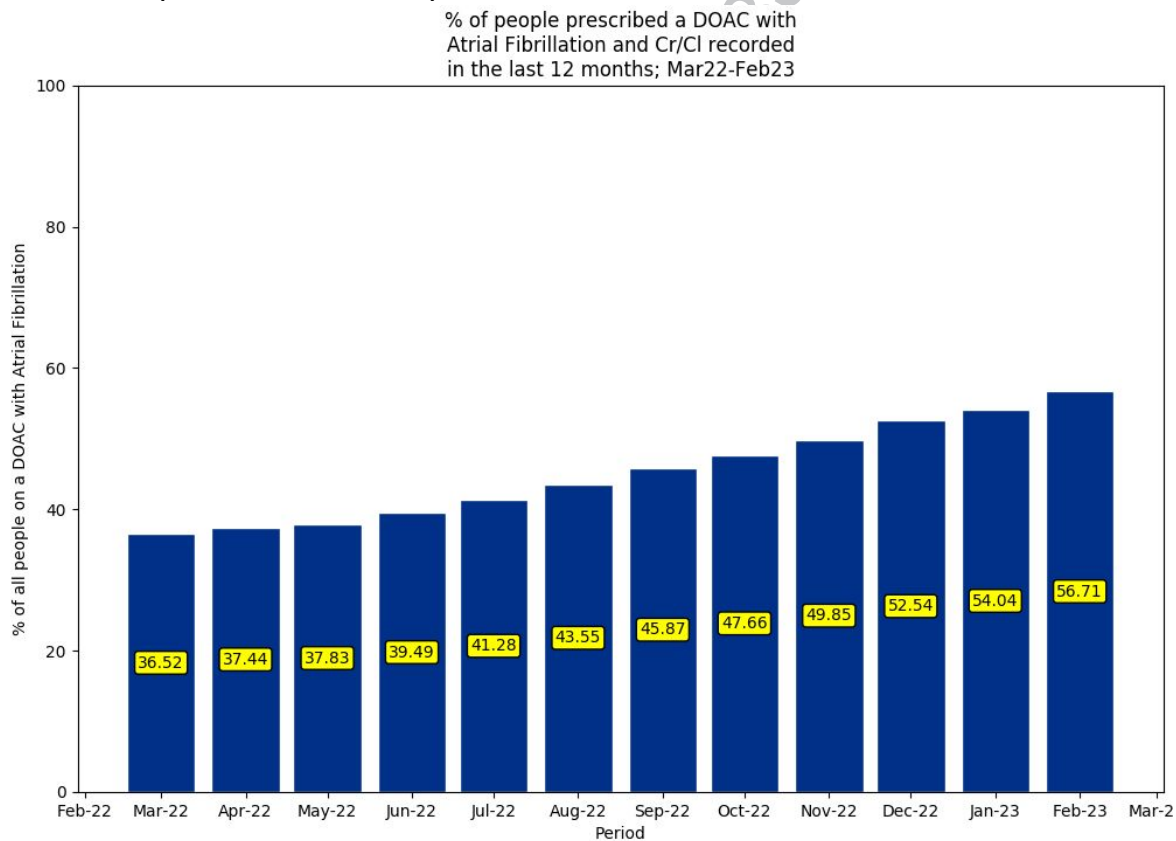
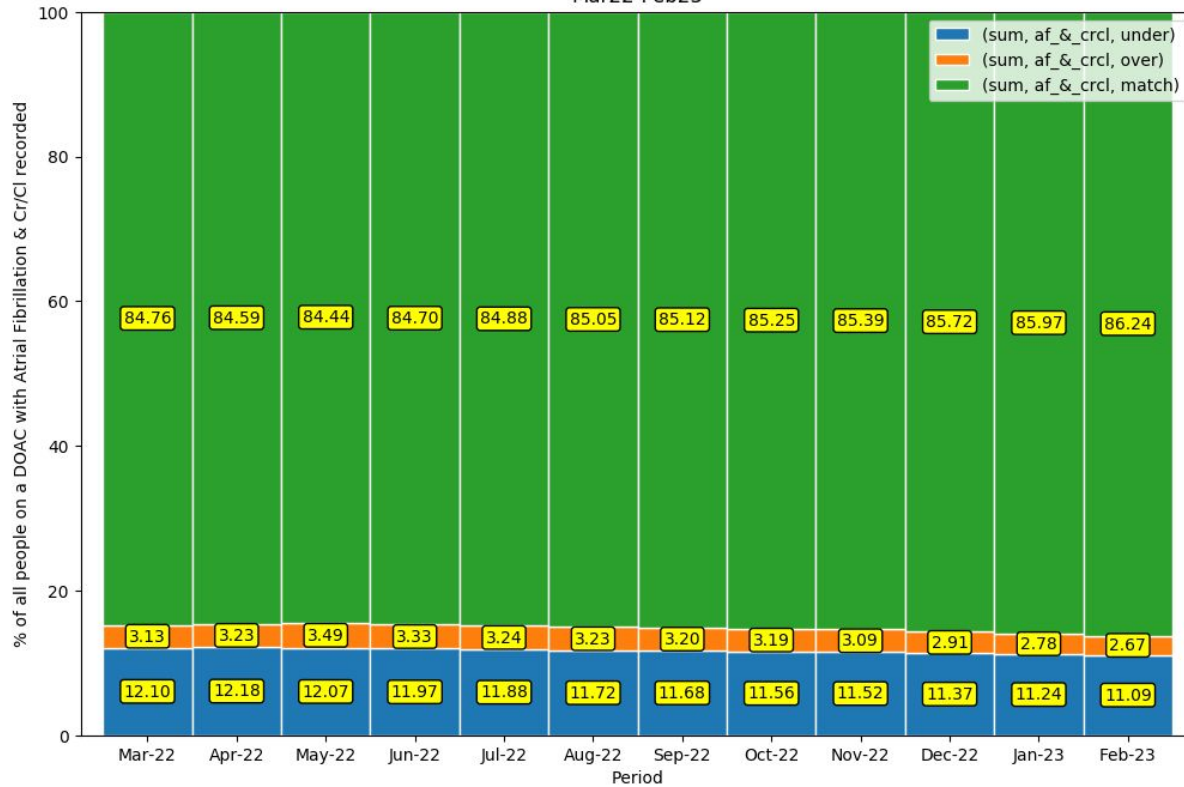


Figure 3 illustrates an increase in the percentage of patients, from 84.8% to 86.2%, where the recommended DOAC dose (calculated using the CrCl recorded within the last 12 months) matched the prescribed dose (match); 13.8% received a non-recommended DOAC dose according to CrCl (2.7% higher than recommended dose (overdose); 11.1% a lower than recommended dose (underdose)).

Figure 3. Percentage of people prescribed a DOAC with AF and with CrCl recorded in the last 12 months where the recommended dose (calculated using recorded CrCl) does not match the prescribed dose in the last 12 months; Mar22-Feb23

% of people prescribed a DOAC with Atrial Fibrillation and with CrCl recorded in the last 12 months, where the recommended dose (calculated using recorded CrCl) does not match the prescribed dose in the last 12 months; Mar22-Feb23



Discussion

Summary

DOAC usage since the COVID-19 pandemic was analysed in this large-scale study of approximately 20.5 million adult electronic health records, covering 40% of general practices in England. The OpenSAFELY-TPP platform enabled the extraction of both recorded AF diagnosis and CrCl to determine the appropriateness of prescribed DOAC doses. There was an increase in DOAC use since the COVID-19 pandemic with increases seen more in males compared to females and in older age groups. Encouragingly, 72.8%, 94.3%, 73.5% of patients had weight, creatinine and CrCl respectively recorded in the last 12 months and the recording of CrCl has increased substantially over this time in patients with AF and CrCl recorded. However, there

remains a significant proportion of people with recorded AF who do not have a CrCl recorded within the previous 12 months. While most people with a recorded AF were prescribed a recommended DOAC dose, 2.7% received a higher than recommended dose (overdose) and 11.1% a lower than recommended DOAC dose (underdose) according to CrCl.

Strengths and limitations

The main strengths of this study are the scale, timeliness and completeness of the underlying data. The OpenSAFELY platform runs analyses across the full, raw, single-event-level medical records of all patients at 40% of all GP practices in England, including all tests, treatments, diagnostic events and other salient clinical and demographic information that has been coded and recorded. Using the OpenSAFELY platform we were able to link a prescription for a DOAC, with recorded AF and CrCl. This presents an opportunity to investigate the safety and efficacy of DOACs prescribed in the cohorts where there is uncertainty or less published data, for example weight <50kg or >120kg, CrCl <15ml/min.

We also recognise some limitations. Only data that is coded in the electronic health record is included in the analysis and so any free text data were not included. This could mean that our analysis has under-reported on parameters entered as free text rather than coded. Reduced face to face consultations may have limited actual body weights being recorded and documented. It is possible that some of the recommended DOAC doses calculated were inappropriate for patients with a dual diagnosis of venous thromboembolism (VTE) and AF, which require different DOAC dosing. In these patients the VTE DOAC dose would be used in preference to the AF dose and therefore dose appropriateness could have been misclassified. Additionally, the appropriate DOAC dosing was calculated using only a patient's recently recorded CrCl. Some DOACs, such as edoxaban have additional criteria that contribute to the dosing recommendation, such as accounting for weight and concurrent treatment with interacting medications which may mean that some doses have been misclassified.⁹

Comparison with existing literature

Prescribing data shows that between January 2018 and February 2023, DOAC prescribing increased from 0.82% to 1.58% of the total English population.¹⁰ This is in line with the findings in this analysis. A previous OpenSAFELY study also found an increase in DOAC prescribing at the outset of the COVID-19 pandemic due to increased switching of anticoagulants from warfarin to DOACs.⁷

Our analysis, which found that 13.8% of people with recorded AF on a DOAC have been prescribed a non-recommended dose for their recorded calculated CrCl, is in line with Khachatryan et al who found that 18.0% of patients prescribed a DOAC received an incorrect dose from data up to March 2021.¹¹ Our analysis has shown a 4.2% decrease in non-recommended DOAC doses which may be due to increased awareness and new targets for general practices through the Investment and Impact Fund (IIF): 2021/22 and 2022/23 SMR-03: Percentage of patients prescribed a DOAC who received a renal function test and a recording of their weight and CrCl, along with a change or confirmation of their medication dose.¹² Overdosing was highest for rivaroxaban which is in line with data in Supplementary Table 1. We found apixaban was highest for underdosing, however, Khachatryan et al found that dabigatran followed by apixaban were highest for underdosing.¹¹ A systematic review of 75 studies showed that most patients treated with DOACs for stroke prevention in AF received doses in accordance with guidelines. However, 25-50% of patients received off-label doses. DOAC overdosing was associated with increased all-cause mortality and worse bleeding events while underdosing was associated with increased cardiovascular hospitalisation, particularly for apixaban, with a nearly 5-fold increased risk of stroke.¹³

Implications for research and/or practice

To the best of our knowledge, this is the first time that the prescribed DOAC dose has been compared to the calculated dose for recorded CrCl to determine whether people may be at increased risk of bleeding or reduced efficacy in stroke prevention from their DOAC in England on this scale since the COVID-19 pandemic.

In our analysis, 316,947 patients were aged 70 years and over. Whilst this data is in line with an expected increase in DOAC prescribing based on national guidance, extra vigilance in the older age group is suggested given the increasing use of DOACs in older patients and the MHRA warning that DOACs should be used with caution in older patients.³

There was a lower percentage of patients with a recorded CrCl compared to eGFR. Whilst NICE DOAC guidance explicitly mentions CrCl ranges, a commonly used measure of renal function is eGFR.^{4,6} However, use of eGFR for dosing of DOACs is known to increase the risk of bleeding events as a consequence of overestimating renal function.⁵ The MHRA advises that CrCl should be considered for dosage adjustment of medicines that are substantially renally excreted and have a narrow therapeutic index. In particular, CrCl should always be used to guide dose adjustment for DOACs.⁵

With the increasing numbers of patients on DOACs in primary care it is important to ensure guidelines are explicit that eGFR and CrCl are not the same nor equivalent measures, and that tools exist to make calculation and recording of CrCl easier for healthcare professionals to document in clinical systems to allow for review, audit and service evaluation. In addition, there is uncertainty whether to use actual or ideal body weight in estimating CrCl.¹⁴ Evidence suggests the Cockcroft-Gault equation is less accurate in extremes of bodyweight (underweight and overweight/obesity).¹⁵ In our study 4,741 patients had a body weight over 120kg and 11,822 had a bodyweight under 50kg (Table 2). For these patients, clarity is needed about which weight to use to calculate CrCl for their DOAC dose.

In England, all general practice clinical systems have sophisticated features to automate certain tasks and provide “clinical decision support” such as automated calculators. Automation of CrCl calculation is complicated by the lack of agreement on which weight to use in the Cockcroft-Gault equation. We think there is an opportunity for national bodies concerned with safety (e.g. MHRA, NICE and NHS England) to collectively identify and update guidelines with which weight is appropriate, amend guidelines to explicitly mention that CrCl is not equivalent to eGFR, and work with GP clinical system suppliers such as TPP to standardise the calculation and recording of CrCl in the electronic health record.

All DOACs should be avoided if CrCl is less than 15ml/min^{4,6} and in our study 3,196 patients had a recorded CrCl of less than 15ml/min (Table 2). These patients should be reviewed and potentially switched to warfarin. Although the majority of patients with recorded AF prescribed a DOAC received the recommended dose according to their CrCl recorded in our analysis, 26,858 patients received an overdose and 6,463 received an underdose according to their recorded CrCl. These people are at higher risk of bleeding and adverse effects due to their overdosing, or of not being protected from developing a stroke or systemic embolism from underdosing. Patients prescribed DOACs inappropriately for their CrCl should have their DOAC reviewed to improve their anticoagulant management.

Conclusion

Throughout the COVID-19 pandemic DOAC prescribing continued to increase with greater increases in males compared to females and in older age groups. Encouragingly, our findings suggest that the recording of CrCl for DOAC patients increased. Most patients with a AF recorded prescribed a DOAC were on the recommended DOAC dose according to their CrCl.

However, a substantial number received either a lower (underdose) or higher (overdose) dose than recommended for their recorded CrCl. Although GPs and other healthcare professionals have a key role in recording CrCl, we recommend that national organisations tasked with safety (e.g. MHRA, NICE and NHS England) should collectively identify and update guidelines with which weight is appropriate to use in the Cockcroft-Gault equation, amend guidelines to explicitly mention that CrCl is not equivalent to eGFR, and work with GP clinical system suppliers such as TPP to standardise the calculation and recording of CrCl in the electronic health record.

Notes

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The views expressed are those of the authors and not necessarily those of the NIHR, NHS England, UK Health Security Agency (UKHSA) or the Department of Health and Social Care. Funders had no role in the study design, collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare the following: BG has received research funding from the Laura and John Arnold Foundation, the NHS National Institute for Health Research (NIHR), the NIHR School of Primary Care Research, NHS England, the NIHR Oxford

Biomedical Research Centre, the Mohn-Westlake Foundation, NIHR Applied Research Collaboration Oxford and Thames Valley, the Wellcome Trust, the Good Thinking Foundation, Health Data Research UK, the Health Foundation, the World Health Organisation, UKRI MRC, Asthma UK, the British Lung Foundation, and the Longitudinal Health and Wellbeing strand of the National Core Studies programme; he is a Non-Executive Director at NHS Digital; he also receives personal income from speaking and writing for lay audiences on the misuse of science. BMK is also employed by NHS England working on medicines policy and clinical lead for primary care medicines data.

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Information governance and ethical approval

NHS England is the data controller for the NHS England OpenSAFELY COVID-19 Service; TPP is the data processor; all study authors using OpenSAFELY have the approval of NHS England.¹⁶ This implementation of OpenSAFELY is hosted within the TPP environment which is accredited to the ISO 27001 information security standard and is NHS IG Toolkit compliant.¹⁷ Patient data has been pseudonymised for analysis and linkage using industry standard cryptographic hashing techniques; all pseudonymised datasets transmitted for linkage onto OpenSAFELY are encrypted; access to the NHS England OpenSAFELY COVID-19 service is via a virtual private network (VPN) connection; the researchers hold contracts with NHS England and only access the platform to initiate database queries and statistical models; all database activity is logged; only aggregate statistical outputs leave the platform environment following best practice for anonymisation of results such as statistical disclosure control for low cell counts.¹⁸

The service adheres to the obligations of the UK General Data Protection Regulation (GDPR) and the Data Protection Act 2018. The service previously operated under notices initially issued in February 2020 by the Secretary of State under Regulation 3(4) of the Health Service (Control of Patient Information) Regulations 2002 (COPI Regulations), which required organisations to process confidential patient information for COVID-19 purposes; this set aside the requirement for patient consent.¹⁹ As of 1 July 2023, the Secretary of State has requested that NHS England

continue to operate the Service under the COVID-19 Directions 2020²⁰ In some cases of data sharing, the common law duty of confidence is met using, for example, patient consent or support from the Health Research Authority Confidentiality Advisory Group.²¹

Taken together, these provide the legal bases to link patient datasets using the service. GP practices, which provide access to the primary care data, are required to share relevant health information to support the public health response to the pandemic, and have been informed that the service operates.

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